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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED OFFICE (DO/US)

PCT/SE00/00755	19 April 2000	19 April 1999
International Application Number	International Filing Date	Priority Date(s) Claimed

NEW PHARMACEUTICAL FORMULATIONS
Title of Invention

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Applicant(s) for DO/US

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Date of Deposit JUNE 19, 2000.
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To the United States Designated Office (DO/US):

I. Accompanying this transmittal letter are certain items which are required under 35 U.S.C. 371 in order that United States National processing of the above identified International application may commence:

(X) at the expiration of the applicable time limit under PCT Articles 22 and 39(1) according to the provisions of 35 U.S.C. 371(b).

( ) as soon as possible upon receipt of this express request under 35 U.S.C. 371(f).

1. The U.S. National fee [35 U.S.C. 371(c)(1)]

a. ( ) was previously transmitted by applicant on (date)____.

b. (**X**) is submitted herewith as follows:

FOR	NO. FILED	NO. EXTRA	SMALL ENTITY RATE	FEE	or	OTHER THAN SMALL ENTITY RATE	FEE
Basic Fee	(USPTO NOT ISA OR IPEA)		////	$485	or	/////	**$970**
Total Claims	-20 =	--	x 9 =		or	x18 =	$
Ind. Claims	**3 - 3**	--	x 39 =		or	x78 =	$
(**X**) Multiple Dependent Claim Presented			+130 =		or	+260 =	**$260**
	TOTAL NATIONAL FEE		$____		or		**$1230**

i. ( ) A check in the amount of $___ is enclosed.

ii. (**X**) Please charge the filing fee, multiple dependent claim fee (if applicable), excess independent claims fee (if applicable), and excess total claims fee (if applicable) **to Deposit Account No. 23-1703**.

iii. (**X**) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to **Deposit Account No. 23-1703**. A duplicate copy of this sheet is enclosed.

(iv) ( ) The filing fee is not enclosed.

2. A copy of the International application as filed [35 U.S.C. 371(c)(2)]:

a. (**X**) is transmitted herewith.

b. ( ) is not required as the application was filed with the United States Receiving Office.

c. ( ) has been transmitted

i. ( ) by the International Bureau. Date of mailing of the application (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed.

ii. ( ) by applicant on (date) _____.

3. A translation of the International application into the English language [35 U.S.C. 371(c)(2)]:

a. ( ) is transmitted herewith.

b. (**X**) is not required as the application was filed in English.

c. ( ) was previously transmitted by applicant on (date)_____.

4. Amendments to the claims of the International application under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) are transmitted herewith.

b. ( ) have been transmitted

i. ( ) by the International Bureau. Date of mailing of the amendments (from form PCT/IB/308): _____.

ii. ( ) by applicant on (date) _____.

c. (**X**) have not been transmitted as

i. ( ) no notification has been received that the International Searching Authority has received the Search Copy.

ii. ( ) the Search Copy was received by the International Searching Authority but the Search Report has not yet issued. Date of receipt of Search Copy (from form PCT/ISA/202): _____.

iii. ( ) applicant chose not to make amendments under PCT Article 19. Date of mailing of Search Report (from form PCT/ISA/210): .

iv. (**X**) the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

5. A Translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) is transmitted herewith.

b. ( ) is not required as the amendments were made in the English language.

c. (X) has not been transmitted for reasons indicated at point I.4.b. or c. above.

6. An executed declaration for patent application of the inventor [35 U.S.C. 371(c)(4)] complying with 35 U.S.C. 115:

a. ( ) was previously submitted by applicant on (date) _____

b. (X) is submitted herewith; and such oath or declaration

i. (X) is attached to the application.

ii. (**X**) identifies the application and any amendments under PCT Article 19 which were transmitted as stated in points 1.2.b. or c. and 1.4. and states that they were reviewed by the inventor as required by 37 CFR 1.70.

c. ( ) will be submitted subsequently.

II. Concerning other documents:

1. An International Search Report or Declaration under PCT Article 17(2)(a):

a. ( ) has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed

b. ( ) is not required as the application was searched by the United States International Searching Authority.

c. ( ) A copy of the International Search Report is transmitted herewith.

d. ( ) has been submitted by applicant on (date) _____.

2. A Statement of prior art under 37 CFR 1.97 and 1.98:

a. ( ) is transmitted herewith including copies of the references cited on the attached form PTO-1449.

b. ( ) will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).

c. ( ) was previously submitted by applicant on _____, in application serial no. _____.

3. (X) An Assignment is transmitted herewith for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

a. (X) Please charge the $40.00 assignment recordation fee to Deposit Account No. 23-1703.

b. ( ) Enclosed is a check in the amount of **$40**.

4. **Other document(s) or information included:**
- Copy of PCT/RO/101 - The PCT Request Form; and a
- Return postcard.

Respectfully submitted,

19 June 2000
DATE

John M. Genova
Reg. No. 32,224

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enclosures

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Abrahamsson et al.
Serial No.	: 09/581,967
Filed	: June 19, 2000
For	: NEW PHARMACEUTICAL FORMULATIONS
Examiner	: To be assigned
Group Art Unit	: To be assigned

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to:
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PRELIMINARY AMENDMENT

Sir:

Preliminary to examination on the merits, please amend the referenced application as follows:

IN THE CLAIMS:

Cancel claims 11-14, 20,21, and 23.

Replace claims 1-6, 9-10, 15-17, 19, and 22 as originally filed with amended claims 1-6, 9-10, 15-17, 19, and 22.

1. (Amended) An oral pharmaceutical formulation comprising therapeutically effective amounts of an inhibitor compound of the ileal bile acid transport system of a patient (IBAT inhibitor compound) and a pharmaceutically acceptable carrier, wherein the formulation is formulated to deliver the IBAT inhibitor compound to the ileum of the patient.

2. (Amended) The oral pharmaceutical formulation according to claim 1, wherein the formulation is formulated to deliver the IBAT inhibitor compound to the ileum by release in the distal jejunum or the proximal ileum.

3. (Amended) The formulation according to claim 1, wherein the carrier is formulated to deliver the IBAT inhibitor compound to the ileum.

4. (Amended) The formulation according to claim 1, wherein the carrier is formulated to release the IBAT inhibitor compound in the distal jejunum or in the proximal ileum.

5. (Amended) The formulation according to claim 1, wherein the carrier is formulated to give a minimum release of the IBAT inhibitor compound in the upper part of the small intestine.

6. (Amended) The formulation according to claim 1, wherein the pharmaceutical formulation is a delayed release formulation.

7. (Not amended herein) The formulation according to claim 6, wherein the formulation provides a lagtime of about 0.5-2 hours after emptying the stomach.

8. (Not amended herein) The formulation according to claim 7, wherein the IBAT inhibitor compound is released during the first hour after the lagtime.

9. (Amended) The formulation according to claim 6, wherein release of the IBAT inhibitor compound from the delayed release formulation is triggered by a pH difference between the jejunum and ileum.

10. (Amended) The formulation according to claim 1, wherein the IBAT inhibitor compound is a low permeability drug as defined in the FDA Biopharmaceutical Classification System.

15. (Amended) A method for the prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, hypercholesterolemia, comprising administering to the subject a therapeutically effective amount of the pharmaceutical formulation as claimed in any one of claims 1 to 10.

16. (Amended) A pharmaceutical formulation for simultaneous, separate or sequential administration for the prophylactic or therapeutic treatment of hypercholesterolemia, comprising therapeutically effective amounts of an inhibitor compound of the ileal bile acid transport system of a patient (IBAT inhibitor compound) and a bile acid binder.

17. (Amended) The pharmaceutical formulation according to claim 16, wherein the IBAT inhibitor compound is a low permeability drug as defined in the FDA Biopharmaceutical Classification System.

18. (Not amended herein) The pharmaceutical formulation according to claim 16, wherein the bile acid binder is a resin.

19. (Amended) The pharmaceutical formulation according to claim 18, formulated to release the bile acid binder in the colon.

22. (Amended) A method for the prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, diarrhea during therapy comprising administration of an IBAT inhibitor compound, comprising administering to the subject a therapeutically effective amount of the pharmaceutical formulation according to any one of claims 16 to 19.

Add new claims 24-27.

24. (New) The oral pharmaceutical formulation according to claim 1, wherein the formulation is formulated to deliver the IBAT inhibitor compound directly in the ileum.

25. (New) A method for enhancing the inhibition of the ileal bile acid transport system of a patient comprising administering to the patient a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1-10.

26. (New) A method for the prophylaxis or therapeutic treatment of hypercholesterolemia comprising simultaneously, separately or sequentially administering therapeutically effective amounts of an inhibitor compound of the ileal bile acid transport system of a patient (IBAT inhibitor compound) and a bile acid binder to the patient in need thereof.

27. (New) A method for the prophylaxis or therapeutic treatment of diarrhea during therapy comprising administration of an inhibitor compound of the ileal bile acid transport system of a patient (IBAT inhibitor compound), comprising administering a therapeutically effective amount of a bile acid binder to the patient in need thereof.

REMARKS

Amendments

Claims 1-6, 9-10, 15-17, 19, and 22 have been amended to place the claims in accordance with U.S. patent practice. Claims 5, 6, and 10 have been amended to remove the dependency of a multiple dependent claim upon another multiple dependent claim. Claim 17 was amended to remove an improper dependency upon claim 10. Claim 22 was amended to correct a typographical error in the dependencies of the claim Claims 11-14, 20-21, and 23 have been canceled.

New claim 24 is directed to an embodiment of the invention deleted form original claim 2. New claim 25 is supported by claims 11 and 12, now canceled. New claim 26 is supported by claims 15 and 16. New claim 27 is supported by claim 23, now canceled.

Applicants submit that no new matter is introduced by any of the amendment to the claims.

Claims 1-2, 4-5, 9-10, 15-19, and 22-Version With Markings to Show Changes Made:

1. An oral pharmaceutical formulation comprising therapeutically effective amounts of an inhibitor compound of the ileal bile acid transport system of a patient (IBAT inhibitor compound) and a pharmaceutically acceptable carrier, wherein the formulation is formulated [designed] to deliver the IBAT inhibitor compound to [in] the ileum of the patient.

2. The oral pharmaceutical formulation according to claim 1, wherein the formulation is formulated [designed] to deliver the IBAT inhibitor compound to [in] the ileum by release in [one or more parts of the body selected from the] the distal jejunum or [and] the proximal ileum [, and/or directly in the ileum].

3. The formulation according to claim 1, wherein the carrier is formulated [designed] to deliver the IBAT inhibitor compound to [in] the ileum.

4. The formulation according to claim 1, wherein the carrier is formulated [designed] to release the IBAT inhibitor compound in the distal jejunum or [and] in the proximal ileum.

5. The formulation according to claim 1 [any one of claims 1 to 4], wherein the carrier is formulated [designed] to give a minimum release of the IBAT inhibitor compound in the upper part of the small intestine.

6. The formulation according to claim 1 [any one of claims 1 to 4], wherein the pharmaceutical formulation is a delayed release formulation.

9. The formulation according to claim 6, wherein release of the IBAT inhibitor compound from the delayed release formulation is triggered by a [the] pH difference[s] between the jejunum and ileum.

10. The formulation according to claim 1 [any one of claims 1 to 9], wherein the IBAT inhibitor compound is a low permeability drug as defined in the FDA Biopharmaceutical Classification System [FDA].

15. A method for the prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, hypercholesterolemia, comprising [which method comprises] administering to the subject a therapeutically effective amount of the pharmaceutical formulation as claimed in [designed according to] any one of claims 1 to 10.

16. A pharmaceutical formulation for simultaneous, separate or sequential administration for [in] the prophylactic or therapeutic treatment of hypercholesterolemia, comprising therapeutically effective amounts of [which formulation comprises] an inhibitor compound of the ileal bile acid transport system of a patient (IBAT inhibitor compound) and a bile acid binder.

17. The pharmaceutical formulation according to claim 16, wherein the IBAT inhibitor compound is a low permeability drug as defined in the FDA Biopharmaceutical Classification System [claim 10].

19. The pharmaceutical formulation according to claim 18, formulated to release [wherein] the bile acid binder in the colon [is in a formulation with colon release].

22. A method for the prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, diarrhea [diarrhoea] during therapy comprising administration of an IBAT inhibitor compound, comprising [which method comprises] administering to the subject a therapeutically effective amount of the [a] pharmaceutical formulation [designed] according to any one of claims 16 to 19 [15 to 18].

CONCLUSION

Upon entry of this Preliminary Amendment, claims 1-10, 15-19, 22, and 24-27 are pending. Applicants respectfully submit the claims 1-10, 15-19, 22, and 24-27 are directed to patentable subject matter. Accordingly, Applicants request allowance of the claims.

Authorization is hereby given to charge any fee in connection with this communication with this communication to Deposit Account No. 23-1703.

Dated: Oct 17, 2001

Respectfully submitted,

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Title: **NEW PHARMACEUTICAL FORMULATIONS**

Reference: H 2036-1 UTL

Inventors: ABRAHAMSSON, Bertil
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NEW PHARMACEUTICAL FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to an oral pharmaceutical dosage form comprising a substance with inhibiting effect on the ileal bile acid transport system (IBAT). More specifically, the dosage form is suitable in the treatment of hypercholesterolaemia. The invention also relates to manufacturing processes and the use of the dosage form in the treatment of hypercholesterolaemia. A further aspect of the invention is the use of a substance with inhibiting effect on IBAT in combination with a bile acid binder by simultaneously, separately or sequentially administration of the two substances, and the use of these substances in the manufacture of such a pharmaceutical dosage form.

BACKGROUND OF THE INVENTION AND PRIOR ART

It is well known that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for coronary heart disease and particularly artherosclerosis. Interfering with the circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous established therapies to reduce the concentration of cholesterol involve for instance treatment with HMG-CoA reductase inhibitors, preferably statins such as simvastin and fluvastin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and cholestipol. One recently proposed therapy involves the treatment with substances with inhibiting effect on the ileal bile acid transport system (IBAT).

Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process, which mainly takes place in the ileum by an active transport mechanism called ileal bile acid transport (IBAT). Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia. See for instance "Interaction of bile acids and cholesterol with

nonsystemic agents having hypocholesterolemic properties", Biochemica et Biophysica Acta, 1210 (1994) 255- 287. Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions.

Several chemical compounds possessing such IBAT activity have recently been described, see for instance hypolipidaemic benzothiazepine compounds described in International Patent Application, Publication No. WO 93/16055 and WO 96/16051; condensed 1,4-thiazepines described in International Patent Application, Publication No. WO 94/18183; different heterocyclic compounds described in International Patent Application, Publication No. WO 94/18184; and 1,4-benzothiazepine-1,1-dioxides described in International Patent Application, Publication No. WO 96/05188, all of which are hereby incorporated by reference.

Further, especially suitable compounds for the present invention are for instance benzothiazepines with IBAT activity described in International Patent Application, Publication No. WO 96/08484; bile acid resorption inhibitors described in International Patent Application, Publication No. WO 97/33882, WO 98/07449 and WO 98/03818, and in European Patent Application, Publication No. EP-A-0864582, EP-A-0489423, EP-A-0549967, EP-A-0573848, EP-A-0624593, EP-A-0624594, EP-A-0624595, and EP-A-0624596, all of which are hereby incorporated by reference. Further compounds of interest can be found in International Patent Application, Publication No. WO 99/32478, WO 99/64409 and WO 00/01687, all of which are hereby incorporated by reference.

It is proposed that these types of compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals. For instance, the dosage forms can be a daily dose which is administered once a day or being divided to be administered several times a day, or alternative in a sustained release form. Suitable dosage forms are intended for oral administration.

All benzothiazepines, however, will not be effective as IBAT inhibitor compounds. Thus, diltiazem, which is a 1,5-benzothaizepine, is a calcium blocker with coronary vasodilating activity (see The Merck Index, Merck & Co, Inc., 12th ed., 1996, p. 541). With respect to inhibition of IBAT, diltiazem has no activity.

In general, pharmaceutical drug substances will be absorbed in the upper small intestine, and therefore only a small amount will reach ileum when administered in a conventional oral dosage form. Irrespective of the construction of the pharmaceutical dosage form, it should provide contact for the active compound, e.g. inhibitor of IBAT, with the compound´s site of action in the body, for example in the ileum. The above prior art documents discuss in general terms suitable pharmaceutical dosage forms for the described IBAT inhibitor compounds. However, none of the documents describe a specific way to obtain a release of the active substance directly to or close to the site of action.

Contact between the active drug and the site of action can be established in different ways. The present application describes a new pharmaceutical dosage form which reduces and minimises absorption, metabolism and dilution in the luminal content of the IBAT inhibitor in the body before the active substance (IBAT inhibitor compound) reaches its site of action.

It has been proposed that after absorption over the gastro-intestinal membrane, an IBAT inhibitor could interact with transport systems similar to IBAT for instance the corresponding transport system in the liver (LBAT) or could provide other non-specific systemic effects which could lead to undesirable pharmacological or even toxicological effects. This could severely limit the clinical usefulness of IBAT inhibitors especially in the treatment of hypercholesterolaemia, i.e. conditions associated with elevated concentra-tions of total cholesterol and low-density lipoprotein cholesterol.

The inhibition of the re-absorption of bile acids from the small intestine performed by an effective IBAT inhibitor may lead to increased levels of bile acids in the lower parts

(colon) of the gastro-intestinal tract. Such an increase of bile acid concentrations in the distal regions could potentially generate diarrhoea and discomfort to the patient. The present invention provides a new approach to minimise the concentration of free bile acids in the colon and thereby reduce the potential risk of adverse events by co-administration of a bile acid binder together with the IBAT inhibitor. However, the combination of an IBAT inhibitor and a bile acid binder have previously been proposed in the above patent applications describing new IBAT inhibitor compounds. The purpose of such previously described combinations have been to enhance the cholesterol lowering efficacy of the therapy, and there is no hint that such a combination could be used to minimise a potential risk for diarrhoea connected with IBAT inhibitor therapy.

BRIEF DESCRIPTION OF THE INVENTION

The aim of the present invention is to reduce the problem with undesirable side effects of IBAT inhibitor compounds by providing a pharmaceutical formulation, which reduces the systemic drug exposure while maintaining or enhancing the cholesterol lowering effect of the drug. Such undesirable systemic effects put a load on other organs, e.g. liver and kidneys. Thus, the present dosage form provides a reduced, i.e. minimum absorption, metabolism and dilution in the luminal content of the IBAT inhibitor by a specific targeting to the site of action. The release is directed specifically to the site of action which reduces or even might avoid toxicological effects of the drug. The formulation is intended to be orally administered and pass through the upper part of the small intestine with a minimum release of the IBAT inhibitor before it reaches the distal jejunum or proximal ileum.

The present invention provides such a dosage form, which delivers the main part of the dose to the site of action, i.e. in the distal jejunum, in the proximal ileum or in the distal ileum. The release of the drug is thereby reduced or minimised to more proximal parts, the duodenum and jejunum, where drug absorption in general is most efficient. Thus, the

release of the drug should preferably start in the distal jejunum or proximal ileum, or the entire dose should be delivered directly to the ileum.

Preferably, the formulation is an orally administered formulation, such as a delayed release formulation, which starts to release the main part of the drug in the distal jejunum or in the proximal ileum. The oral formulation might also provide protection of the drug from the acid environment in the stomach by an enteric coating. Such an enteric coating also protects the gastric mucosa from drug exposure and thereby minimises irritation or even damages of the gastric mucosa potentially caused by aggressive drug exposure.

An additional aim of the present invention is to provide a combination for simultaneous, separate or sequential administration which combination comprises an IBAT inhibitor and a bile acid binder. Such a combination will protect the patient from any possible side effect caused by excess of bile acids in the colon, such as diarrhoea. If the transport of bile acids is blocked by an IBAT inhibitor the bile acids might be deposited in the colon and induce a secretory diarrhoea - by irritation and inflammation - as a undesired side effect caused by the treatment with an IBAT inhibitor.

Another aspect of the provided combination therapy is that the bile acid binder, for instance a resin such as cholestyramine or cholestipol, could preferably be administered in a dosage form with colon release of the bile acid binder. A colon release formulation will provide protection of the bile acid binder to the luminal contents in the more proximal parts of the intestine, where the bile acid concentrations are high. Such a formulation will prevent binding of bile acids to the bile acid binder before the formulation reaches the colon. Thereby, maximal bile acid binding capacity will be obtained in the colon and any possible gastro-intestinal side effects, such as diarrhoea, may be avoided. Thus, any additional amount of bile acid presented in the colon due to the treatment with the IBAT inhibitor compound, would be bound to a bile acid binder, which the bile acid binder is preferably delivered in the colon, thereby any possible side effects such as diarrhoea is avoided.

DETAILED DESCRIPTION OF THE INVENTION

IBAT inhibitor compounds

Active ingredients suitable as IBAT inhibitor compounds in the present invention are those exhibiting activity when screening for IBAT inhibiting properties. Suitable examples of such compounds can be found in the references cited on page 2 of the present application.

Active ingredients particularly suitable as IBAT inhibitor compounds in the present invention include benzothiazepines, and more particularly 1,4-benzothiazepines and 1,5-benzothiazepines exhibiting activity when screening for IBAT inhibiting properties. Of these, compounds with an oxidized sulfur group, particularly a sulfone group, in the 7 membered ring are preferred. Furthermore, the presence of an amine group in the 7 membered ring is preferred.

Pharmaceutical formulations

According to one aspect of the invention, an orally administered pharmaceutical formulation of an IBAT inhibitor compound is provided, which formulation releases almost the entire dose of the IBAT inhibitor compound in the distal jejunum, in the proximal ileum, or deliver the dose directly to the ileum. Such a formulation will minimise drug release in the upper part of the small intestine, i.e. above distal jejunum.

Optimal drug release and drug binding in the ileum can for instance be obtained by a delayed release formulation, such as a formulation with a specified lagtime. More specifically, less than 30 % of the drug could be released during the time the formulation spends in the stomach and in the proximal small intestine, i.e. during the passage of the upper part of the small intestine.

Thus, according to a second aspect, the present invention provides a pharmaceutical formulation with a delayed release of the IBAT inhibitor compound by a controlled lagtime. The main part of the formulation shall pass the duodenum and jejunum with a minimum release of the active dose, and thereby increasing the dose available for binding to the site of action in the ileum and thereby increasing the inhibition of the ileal bile acid transport system. Preferably, the lagtime period is about 0.5 - 2 hours calculated from emptying from the stomach, and more than 70 % of the dose should be released approximately during the next 0.5 - 2.0 hours, i.e. after the lagtime period. More preferably, the dose should be released during the first hour after the lagtime period.

Dosage forms with a controlled lagtime can be constructed in different ways for instance as described in the following.

A controlled lagtime can be triggered by pH changes, redox potential differences or luminal metabolic changes in the gastro-intestinal tract as described in Aliment Pharmacol Ther 1997, 11 (suppl 3): 109-115. Such a controlled lagtime could be obtained for instance by a programmed disintegration of the formulation due to erosion, dissolution or in general by components present in the formulation interacting with the environment in the gastro-intestinal tract. Preferably, the drug release from the dosage form could be triggered by the pH variation between jejunum and ileum.

Alternatively, the drug release from the dosage form can be chronographic controlled to obtain the above specified time limits, such as for instance described in the European Patent Application, Publication No. EP-A-0384642.

When the formulation reaches the distal jejunum or the ileum, the drug release should preferably be either immediately, with a sustained release or be based on a combination of such release principles. The duration of the drug release for a sustained release formulation should preferably not exceed 2 hours.

According to a third aspect of the invention, a sustained release formulation can be constructed by any known principle, such as eroding or non-eroding matrices, membrane-coating layers or by diffusion or osmotically driven drug release. Suitable techniques for the construction of such formulations are for instance described in M. E. Aulton, Pharmaceutics, The science of dosage form design. (1988).

An additional aspect of the invention is to combine an IBAT inhibitor compound with a bile acid binder thereby avoiding a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such as diarrhoea in patients during therapy comprising IBAT inhibitor compounds.

Suitable bile acid binders for such a combination therapy are resins, such as cholestyrmine and cholestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutical dose for treatment of cholesterolemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

A further aspect in connection with such a combination therapy is that the bile acid binder could be administered in a dosage form with colon release, i.e. delivery of the active dose of bile acid binder in the colon. A possible risk of receiving an excess of bile acid in the colon by treatment with an IBAT inhibitor could be avoided by co-administration of a bile acid binder with colon release. Thus, any excess of bile acid in the colon, with a possible risk to cause diarrhoea, will be bound into a resin. The dose of the bile acid binder could be kept low due to an effective use of the dose by such a colon release. The colon delivery of the bile acid binder can be obtained by a formulation comprising a core containing the bile acid binder and optionally pharmaceutically acceptable excipients, and a coating of said core with a delayed release membrane adapted for colonic delivery. Technologies to obtain

such a delivery of drugs to the colon are for example described in Drug Development and Industrial Pharmacy 1997, 23: 893-913.

Further general aspects of the invention are that the formulations can be solid, semi-solid or liquid formulations. In a solid formulation, the carrier can be monolithic, such as tablets or capsules. One preferred monolithic formulation is a coated tablet, a capsule comprising small, coated units or a multiple unit tablet comprising a multitude of small coated units. Semi-solid or liquid formulations can be administered in capsules suitable for such vehicles. The most preferred formulation is an oral formulation such as a tablet or a capsule comprising coated small units or pellets. The formulation or dosage form may contain from 0.05% to 95% of the active compound in admixture with a pharmaceutically acceptable carrier, or pharmaceutically acceptable excipients.

Preparation of core material

The core material for the units, i.e. the tablets or the individual pellets can be constituted according to different principles. The core material may be homogenous or heterogeneous. The core containing the active principle may be differently formulated such as monolithic tablets, capsules, granules, pellets, other particles or crystals.

With a homogenous core material is meant, that it has a homogenous distribution of active substance throughout the core material.

The active substance, i.e. the IBAT inhibitor compound, is optionally mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Such components can be binders, surfactants, lubricants, glidants, fillers, additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

Said core material may be produced either by direct compression of the mixed ingredients, or by granulation of the ingredients followed by compression of the granulated material.

In direct compression, the ingredients are mixed and compressed by using ordinary tableting equipment.

For the granulation there are numerous alternatives of granulating procedures mentioned in the literature, dry methods like roller compaction (Chilsonator) and wet methods utilizing granulating solutions with and without the addition of binders. A variant of the wet methods is to make a spray-granulation in a fluid bed.

For the wet granulating methods, either organic solvents, aqueous solutions or pure water may be utilized to prepare the granulating solutions. Due to environmental considerations pure water is preferred, if it is possible due to the composition of the mixture.

Homogenous core particles can also be prepared by techniques such as dry or wet milling, freeze milling, air-jet micronisation, spray drying, spray chilling, controlled crystallisation, supercritical crystallisation, emulsion solvent evaporation and emulsion solvent extraction.

The core material may also be produced by extrusion/spheronization, balling or compression, utilizing different process equipments.

The size of the formulated core materials is approximately between 2 and 14 mm, preferably between 3 and 9 mm for a tablet preparation, and between 0.001 and 4 mm, preferably between 0.001 and 2 mm for a pellet preparation.

The manufactured core material may be further layered with additional ingredients comprising the active substance and/or be used for further processing.

Alternatively, the core material may be heterogeneous with an inner zone, for instance a seed or sphere, not containing the active substance. A layer comprising the active

substance, and optionally pharmaceutically acceptable excipients, surrounds this seed or sphere.

The seed or sphere may be soluble or insoluble. Optionally, the seed or sphere (inner zone) may be coated with an inert layer to prepare a smooth surface before the layer containing active substance is applied onto the seed/sphere.

Insoluble seeds/spheres may comprise different oxides, celluloses, organic polymers and other materials, alone or in mixtures. Water-soluble seeds/spheres may comprise different inorganic salts, sugars and other materials, alone or in mixtures. The size of the seeds may vary between approximately 0.1 and 2 mm. The seeds layered with the matrix containing the active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

Processes for application of delayed release membranes

Delayed release membrane can be applied to the core material, being a monolithic tablet, multiple units or a hard or soft gelatine capsule, by coating or layering procedures in suitable equipment such as coating pans, coating granulators or in a fluidized bed apparatus using water and/or organic solvents for the coating process. Also powder-coating principles may be applied. Another possibility is to apply the coating by microencapsulation techniques such as coacervation, emulisification with subsequent removal of the solvent by extraction or evaporation, ionotropic gelation or congealing.

Such delayed release membranes may be applied on core material comprising the IBAT inhibitor for delivery to the distal small intestine and optionally also be applied to the bile acid binder for delivery to the colon.

Pharmaceutical additives

Delayed release coatings may be obtained by one or more, separetely or in compatible combinations of pharmaceutically acceptable ingredients, in amounts carefully titrated to reach the intended release properties. As coating layer, the following pH sensitive polymers can be applied; e.g. methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethyl-cellulose, shellac or other suitable enteric coating layer polymer(s). The coating layer may also be composed of film-forming polymers being sensitive to other luminal components than pH, such as bacterial degradation or a component that has such a sensitivity when it is mixed with another film-forming polymer. Examples of such components providing delayed release to the intended regions are; polymers comprising azo bond(s), polysaccharides such as pectin and its salts, galactomannans, amylose and chondroitin, disulphide polymers and glycosides.

The delayed release coating or an additional coating of the formulation may contain other film-forming polymers being non-sensitive to the luminal conditions for technical reasons or chronographic control of the drug release. Materials to be used for such purpose includes, but are not limited to; sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures.

Additives such as dispersants, colorants, pigments, additional polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the coating layer. Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the core material.

The coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, glycerol monoesters, polysorbates or other plasticizers and mixtures thereof. The amount of plasticizer is preferably optimised for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

In preparation of tablets, either as monolithic drug containing cores for subsequent coating with a delayed release membrane or as a matrix for coated multiple units, additional ingredients may be needed to obtain suitable technical properties such as binders, disintegrants, bulk agents, glidants, lubricants, and coatings agents without effects on the drug release such as water soluble polymers, anti-tacking agents, colourants, pigments and waxes. Ingredients well known for such usage are for example described in "Handbook of pharmaceutical excipients", 2nd edition, 1994, Pharmaceutical Press, London.

Preparation of final dosage forms

Coated units may be filled into hard gelatine capsules or mixed with tablet excipients, such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives, and be compressed into tablets. The compressed tablet is optionally covered with film-forming agents to obtain a smooth surface of the tablet and further enhance the mechanical stability of the tablet during packaging and transport. Such a tablet coat, which may be applied on a multiple unit tablet or a conventional tablet, may further comprise additives like anti-tacking agents, colourants and pigments or other additives to improve the tablet appearance.

Suitable drugs for the new formulations are IBAT inhibitor compounds such as described in the above-discussed documents, hereby incorporated by references.

The IBAT inhibitor compound could alternatively be a low permeability drug as defined in the Biopharmaceutical Classification System proposed by FDA.

A combination therapy according to the invention should preferably comprise simultaneously, separately or sequentially administration of an IBAT inhibitor compound and a bile acid binder. The IBAT inhibitor could preferably be formulated for ileum delivery and the bile acid binder could preferably be formulation for colon release.

Medical and pharmaceutical use of the invention

The pharmaceutical formulations according to the present invention can be used in the treatment of hypercholesterolaemia. A suitable unit dose will vary with respect to the patients body weight, condition and disease severity. The dose will also depend on if it is to be used for prophylaxis or in the treatment of severe conditions, as well as the route of administration. The daily dose can be administered as a single dose or divided into two or more unit doses. An orally administered daily dose of an IBAT inhibitor is preferably within 0.1 – 1,000 mg, more preferable 1 - 100 mg.

A pharmaceutical formulation according to the present invention with a targeted delivery in the gastro intestinal tract provides a reduced systemic exposure, as can be measured by the area under the drug plasma concentration versus time curve (AUC), while maintaining or even increasing the therapeutic effect, as e.g. measured by serum cholesterol reduction.

A combination therapy comprising an IBAT inhibitor and a bile acid binder comprises preferably a low daily dose of the bile acid binder, such as less than 5 g of a resin, and more preferably less than 2 g. A dosage form with colon release of the bile acid binder could be constructed by any of the above described principles for delayed release formulations.

The following contemplated Examples are intended to illustrate, but in no way limit the scope of the invention.

EXAMPLES

Example 1

A formulation having the following composition can be prepared:

	amount/capsule (mg)
IBAT inhibitor compound (1,5-benzothiazepine)	10
Non pareil spheres	500
Ethyl cellulose	2
Hydroxypropylmethyl cellulose	10
Eudragit L100-55	25
Triethylcitrate	2.4

The active drug can be dissolved together with ethyl cellulose and hydroxypropyl cellulose in ethanol 99 %. The mixture can then be sprayed onto the non-pareil spheres in a fluidized bed apparatus. Thereafter, the pellets can be dried and aerated to remove residual ethanol. The Eudragit L100-55 dispersion with addition of triethyl citrate can then be sprayed onto the drug beads in a fluidized bed apparatus. Subsequently, the coated beads can be filled in hard gelatine capsules after drying and sieving.

Example 2

A formulation having the following composition can be prepared:

	amount/tablet (mg)
IBAT inhibitor compound (1,5-benzothiazepine)	10
Silicon dioxide	200
Povidone K-25	20
Eudragit FS30D	30
Microcrystalline cellulose	250
Sodium stearyl fumarate	5

The active drug can be suspended in water and sprayed onto silicon dioxide cores of a predefined size in a fluidized bed apparatus. The drug pellets can be dried in an oven at 40° C for 24 h. Thereafter, a layer of Povidone K-25 can be applied on the beads from an ethanolic solution in a fluidized bed apparatus. A final coat of Eudragit FS30D dispersion can be applied thereafter in a fluidized bed. The coated beads can be mixed with microcrystalline cellulose and sodium stearyl fumarate in a mixer and subsequently compressed to tablets.

CLAIMS

1. An oral pharmaceutical formulation comprising an inhibitor compound of the ileal bile acid transport (IBAT inhibitor compound) and a pharmaceutically acceptable carrier, wherein the formulation is designed to deliver the IBAT inhibitor compound in the ileum.

2. The oral pharmaceutical formulation according to claim 1, wherein the formulation is designed to deliver the IBAT inhibitor compound in the ileum by release in one or more parts of the body selected from the distal jejunum and proximal ileum, and/or directly in the ileum.

3. The formulation according to claim 1, wherein the carrier is designed to deliver the IBAT inhibitor compound in the ileum.

4. The formulation according to claim 1, wherein the carrier is designed to release the IBAT inhibitor compound in the distal jejunum and in the proximal ileum.

5. The formulation according to any one of the claims 1 to 4, wherein the carrier is designed to give a minimum release of the IBAT inhibitor compound in the upper part of the small intestine.

6. The formulation according to any one of claims 1 to 4, wherein the pharmaceutical formulation is a delayed release formulation.

7. The formulation according to claim 6, wherein the formulation provides a lagtime of about 0.5 - 2 hours after emptying the stomach.

8. The formulation according to claim 7, wherein the IBAT inhibitor compound is released during the first hour after the lagtime.

9. The formulation according to claim 6, wherein release of the IBAT inhibitor compound from the delayed release formulation is triggered by the pH differences between the jejunum and ileum.

10. The formulation according to any one of claims 1 to 9, wherein the IBAT inhibitor compound is a low permeability drug as defined in the Biopharmaceutical Classification System FDA.

11. The use of a pharmaceutical formulation comprising an IBAT inhibitor compound with targeted delivery in the gastro-intestinal tract according to any one of the claims 1 to 10 to reduce systemic exposure.

12. The use of a pharmaceutical formulation comprising an IBAT inhibitor compound with targeted delivery in the gastro-intestinal tract according to any one of the claims 1 to 10 to enhance the therapeutic effect.

13. The use of a pharmaceutical formulation according to any one of the claims 1 to 10 in the treatment of hypercholesterolemia.

14. The use of a pharmaceutical formulation according to any one of the claims 1 to 10, in the manufacture of a medicament for the prophylactic or therapeutic treatment of hypercholesterolemia.

15. A method for prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, hypercholesterolemia, which method comprises administering to the subject a pharmaceutical formulation designed according to any one of claims 1 to 10.

16. A pharmaceutical formulation for simultaneous, separate or sequential administration in the prophylactic or therapeutic treatment of hypercholesterolemia, which formulation comprises an IBAT inhibitor compound and a bile acid binder.

17. The pharmaceutical formulation according to claim 16, wherein the IBAT inhibitor compound is a low permeability drug as defined in claim 10.

18. The pharmaceutical formulation according to claim 16, wherein the bile acid binder is a resin.

19. The pharmaceutical formulation according to claim 18, wherein the bile acid binder is in a formulation with colon release.

20. The use of a pharmaceutical formulation according to any one of claims 16 - 19 in the treatment of diarrhoea during therapy comprising an IBAT inhibitor compound.

21. The use of a pharmaceutical formulation according to any one of the claims 16 to 20, in the manufacture of a medicament for the prophylactic or therapeutic treatment of hypercholesterolemia.

22. A method for prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, diarrhoea during therapy comprising an IBAT inhibitor compound, which method comprises administering to the subject a pharmaceutical formulation designed according to any one of claims 15 to 18.

23. The use of a bile acid binder as prophylaxis or in the treatment of diarrhoea during therapy comprising an IBAT inhibitor compound.

ABSTRACT

An oral pharmaceutical formulation comprising an inhibitor compound of the ileal bile acid transport (IBAT inhibitor compound) and a therapeutically acceptable carrier characterised in that the formulation is designed to deliver the IBAT inhibitor compound in the ileum. The IBAT inhibitor compound can also be administered in combination with a bile acid binder to alleviate possible side effects of therapy with IBAT inhibitor compounds, such as for instance diarrhoea. The bile acid binder may be formulated for colon release.

2036 US

Docket Number (Optional) H 2036-1 US

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled NEW PHARMACEUTICAL FORMULATIONS

the specification of which is attached hereto unless the following box is checked:

☒ was filed on 19 April 2000 as United States Application Number or PCT International Application Number SE00/00755 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

			Priority Not Claimed
9901387-2	Sweden	19 April 1999	☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number	(Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believe to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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